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EXAMINER

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ART UNIT PAPER NUMBER

1634

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/914,603
Filing Date: January 09, 2002
Appellant(s): THOMAS ET AL.

Yonggang Ji
For Appellant

EXAMINER'S ANSWER

Ku

This is in response to the appeal brief filed September 12, 2005.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Claimed Subject Matter*

The summary of claimed subject matter contained in the brief is correct.

(6) *Grounds of Rejection to be Reviewed on Appeal*

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6268147	Beattie et al.	July 2001
5484701	Cocuzza et al.	January 1996

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

For the above reasons, it is believed that the rejections should be sustained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6-13, 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Beattie et al. (US Pat. 6,268,147, July 2001).

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Beattie et al. (herein referred to as Beattie) teaches a method of nucleic acid analysis using tandem hybridization on color-coded microspheres and flow cytometric detections (Example 18)(limitations of Claim 14). Beattie teaches that the stacking hybridization approach is applicable to "bead technology" where different capture probe sequences are tethered to microspheres which are distinguishable by any measurable (detectable) unique physical or chemical property associated with each bead, such as size, shape, mass, spectral profile, chemical reactivity, electronic properties, etc (col. 38, lines 35-43)(limitations of Claim 8-12, 16-17). Beattie teaches that the nucleic acid analyte is annealed with a labeled stacking probe of sequence and length designed to bind to a unique position within the analyte nucleic acid (col. 38, lines 60-64). Beattie teaches that expressed sequence-specific stacking and capture probes may be used with RNA or cDNA analyte, the relative level of label bound to each color-coded bead will provide a gene expression (transcriptional profile)(limitations of Claims 2-3). As seen in Figure 15A and 15B, the target is labeled with a longer labeled stacking probe or a short labeled probe allele-specific or expressed sequence specific (limitations of Claim 6, 7). For genotyping and mutation analysis, allele specific capture probes are hybridized with genomic DNA or mixture of PCR products, preannealed with a mixture of stacking probes. The quantity of label associated with each color-coded bead is quantitatively determined using flow cytometry with spectral analysis of individual beads streaming past the detector window (col. 39, lines 5-10)(limitations of Claim 4). Beattie teaches that the stacking probe must be labeled with a tag that is distinguishable from the spectral properties of color-coded beads. If dual labels are used (one used with a

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reference sample and another used with a test sample) the two samples are hybridized with a mixture of color-coded beads, and the relative binding of the two labels from the stacking probes to each color-coded bead will reveal the two transcriptional profiles (col. 39, lines 15-25)(limitations of Claim 13). Beattie teaches that for gene expression profiling, each expressed sequence is represented by a specific capture probe tethered to a color-coded bead, plus a labeled probe which hybridizes in tandem with the capture probe. The level of label bound to each color-coded bead reveals the transcriptional provide. The reference and test transcriptional profiles may be compared (col. 40, lines 10-15). Beattie teaches that a high degree of multiplexing is provided by the use of color-coded beads (col. 40, lines 22-25). Thousands of different color codes can be distinguished using several fluorescent dyes mixed together in defined ratios at different levels, providing a large number of distinct spectral profiles (col. 40, lines 25-30). Beattie teaches that as long as the labels associated with the stacking probes are distinguishable from those of the "coded" beads, a wide variety of physical or chemical properties may be incorporated into microsphere to enable alternative bead-identifying detection schemes (col. 40, lines 30-35).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al. (US Pat. 6,268,147, July 2001) in view of Cocuzza et al. (US Pat. 5,484,701, January 1996).

Beattie et al. (herein referred to as Beattie) teaches a method of nucleic acid analysis using tandem hybridization on color-coded microspheres and flow cytometric detections (Example 18)(limitations of Claim 14). Beattie teaches that the stacking hybridization approach is applicable to "bead technology" where different capture probe sequences are tethered to microspheres which are distinguishable by any measurable (detectable) unique physical or chemical property associated with each bead, such as size, shape, mass, spectral profile, chemical reactivity, electronic properties, etc (col. 38, lines 35-43)(limitations of Claim 8-12, 16-17). Beattie teaches that the nucleic acid analyte is annealed with a labeled stacking probe of sequence and length designed to bind to a unique position within the analyte nucleic acid (col. 38, lines 60-64). Beattie teaches that expressed sequence-specific stacking and capture probes may be used

with RNA or cDNA analyte, the relative level of label bound to each color-coded bead will provide a gene expression (transcriptional profile)(limitations of Claims 2-3). As seen in Figure 15A and 15B, the target is labeled with a longer labeled stacking probe or a short labeled probe allele-specific or expressed sequence specific (limitations of Claim 6, 7). For genotyping and mutation analysis, allele specific capture probes are hybridized with genomic DNA or mixture of PCR products, preannealed with a mixture of stacking probes. The quantity of label associated with each color-coded bead is quantitatively determined using flow cytometry with spectral analysis of individual beads streaming past the detector window (col. 39, lines 5-10). Beattie teaches that the stacking probe must be labeled with a tag that is distinguishable from the spectral properties of color-coded beads. If dual labels are used (one used with a reference sample and another used with a test sample) the two samples are hybridized with a mixture of color-coded beads, and the relative binding of the two labels from the stacking probes to each color-coded bead will reveal the two transcriptional profiles (col. 39, lines 15-25)(limitations of Claim 13). Beattie teaches that for gene expression profiling, each expressed sequence is represented by a specific capture probe tethered to a color-coded bead, plus a labeled probe which hybridizes in tandem with the capture probe. The level of label bound to each color-coded bead reveals the transcriptional provide. The reference and test transcriptional profiles may be compared (col. 40, lines 10-15). Beattie teaches that a high degree of multiplexing is provided by the use of color-coded beads (col. 40, lines 22-25). Thousands of different color codes can be distinguished using several fluorescent dyes mixed together in defined ratios at different

levels, providing a large number of distinct spectral profiles (col. 40, lines 25-30).

Beattie teaches that as long as the labels associated with the stacking probes are distinguishable from those of the "coded" beads, a wide variety of physical or chemical properties may be incorporated into microsphere to enable alternative bead-identifying detection schemes (col. 40, lines 30-35).

Beattie does not specifically teach immobilizing probes on beads using biotin and streptavidin-coated beads.

However Cocuzza teaches oligonucleotides may be immobilized on a bead using biotin /streptavidin-complexes. Cocuzza teaches that the biotin-avidin (streptavidin) system is a very useful analytical tool (col. 2, lines 5-8). The avidin and streptavidin form an exceptionally tight complex with biotin. Cocuzza teaches that the complexation is effectively an irreversible process (col. 2, lines 23-25).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have immobilized the oligonucleotide probes of Beattie onto beads using the well known method of using biotin/streptavidin for immobilization taught by Cocuzza. The ordinary artisan would have been motivated to have immobilized polynucleotides using the biotin/streptavidin system for the expected benefit of tight complexes and ease of use, as taught by Cocuzza.

(10) Response to Argument

Claims 1-4, 6-13, 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Beattie et al. (US Pat. 6,268,147, July 2001).

Response to Arguments

The appellant traverses the rejection. The appellant asserts Beattie does not teach each and every limitation of the claims of the present invention since Beattie fails to disclose a method comprising “providing the nucleic acids from two sources as labeled probes” (page 5, para 2 of brief). This argument has been reviewed but is not convincing because the claims are broadly drawn to methods which encompass the “labeled stacking probes” of Beattie. The claims are drawn to “comprising methods” and thus encompass additional elements. Specifically, the claims require providing nucleic acids from two sources as labeled probes wherein the nucleic acids from each source is labeled with a distinct marker, forming pools comprising beads which are distinguishable, incubating and analyzing. As stated previously Beattie contemplates, “if dual labels are used (one used with a reference sample and another used with a test sample) the two samples are hybridized with a mixture of color-coded beads, and the relative binding of the two labels from the stacking probes to each color-coded bead will reveal the two transcriptional profiles (col. 39, lines 15-25).” The claims do not exclude the use of a label on the stacking probes, a third probe, for example.

Beattie discloses for genotyping and mutation analysis, allele specific capture probes are hybridized with genomic DNA or mixture of PCR products, preannealed with a mixture of stacking probes. Thus, Beattie teaches taking a sample of test and references samples and hybridizing them with stacking probes (col. 39). The stacking probes for each of the samples are different, i.e. two labels are used. Thus, the reference sample comprises one label and the test sample comprises a separate label.

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Therefore, the samples are differentially labeled with a distinct marker. Then given these two different sources that are labeled with different markers, bead analysis is performed. The relative binding of the two labels (from stacking probes) to each color-coded bead will reveal the two transcriptional profiles simultaneously. Much like applicant's invention, the nucleic acids are prepared from control and test cells and labeled with fluorescent tags. Since the hybrid of stacking probe and sample are hybridized prior to bead analysis, the hybrid would clearly constitute a labeled probe. Therefore, Beattie does teach a method using the nucleic acids from two sources as labeled probes since the hybrid of a stacking probe and a sample would constitute a labeled probe.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al. (US Pat. 6,268,147, July 2001) in view of Cocuzza et al. (US Pat. 5,484,701, January 1996).

Response to Arguments

The response traverses the rejection. The response asserts that "there is a fundamental difference between the current invention and that of Beattie." This argument has been reviewed but is not convincing because the claims are broadly encompass methods comprising the recited steps and do not exclude the use of hybridization of three nucleic acid molecules. Thus for the reasons above and those already of record, the rejection is maintained.


JEANINE A. GOLDBERG
PRIMARY EXAMINER

Respectfully submitted,

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Art Unit 1634

September 26, 2005

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